

Smallpox

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With recent events, the threat of bioterrorism has become a reality. In late 2001, multiple cases of cutaneous and inhalation anthrax were spread through the US mail. On the front line were dermatologists who diagnosed the first cases of cutaneous anthrax in New York City. Since then, physicians who are unsure if they are facing a new form of bioterrorism frequently have consulted dermatologists to evaluate rashes. Because most biological weapons (anthrax, tularemia, plague, smallpox) can have cutaneous manifestations, dermatologists will continue to have an important role in evaluating these potential threats.

Smallpox is probably the most feared biological weapon because of its high mortality rate and ease of spread.¹ In this article, we review diagnostic signs of smallpox and information about vaccination and available treatments.

Background

Smallpox (*variola major*, *variola minor*) is a DNA virus in the genus *Orthopoxvirus*.^{2,3} Smallpox has no animal or insect reservoir and is passed from human to human through droplet aerosol.^{2,3} The word *variola*, which came into use in the 6th century, is derived from the Latin *varius* (spotted) or *varus* (pimple).⁴ With the appearance of syphilis (the great pox) in the late 15th century, people began to use the prefix *small* to distinguish *variola*.⁴ Smallpox can occur as either *variola major* (30% mortality rate) or *variola minor* (milder symptoms and 1% mortality rate).^{2,3,5}

In 1977, smallpox was effectively eradicated through a massive vaccination program conducted

by the World Health Organization (WHO).^{1,2} Recent events have raised the possibility that smallpox could be used as a weapon of bioterrorism with devastating effects. Of paramount importance is that physicians recognize the signs of potential smallpox infection. The mortality rate for smallpox is 30%.^{2,3,5} Smallpox aerosolizes well, and its infectious dose is small—only a few virions.² A single case of suspected smallpox should be treated as an international emergency and must be brought to the attention of health officials.^{2,3}

Before 1970, smallpox was prevalent worldwide, and a majority of people became infected during their lifetime.² Vaccination programs were discontinued when risk of death from vaccination became more likely than infection with smallpox (1 death/1 million vaccinations).⁵ Because routine vaccinations were stopped 30 years ago,⁶ the potential for devastation from smallpox is greater than ever in the United States. One hundred fourteen million Americans younger than 30 years are unprotected.^{2,3} Fewer than half the people in the world have been vaccinated or exposed to smallpox.⁶ Without vaccination, humans are universally susceptible to smallpox.^{1,5}

The former Soviet Union's development of smallpox as a weapon of mass destruction¹ and the post-Soviet Union lack of financial support to keep bioweapons laboratories operating has led to fear that stocks of smallpox will be used by bioterrorists.² Former Soviet researchers have alleged that smallpox was produced in large quantities and adapted for use as a bioweapon.² In 1999, a WHO committee recommended destroying the last remaining stocks of smallpox, held at the US Centers for Disease Control and Prevention in Atlanta, Georgia, and at the Institute of Viral Preparations in Moscow, but neither the United States nor Russia has implemented this recommendation.²

Transmission

Contact of a few virions of smallpox with the respiratory mucosa can lead to infection.² Aerosol release of a small amount of smallpox could infect 100 people; the virus would spread rapidly, and, with no one having immunity, secondary cases

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would expand 10 to 20 times with each generation of infection.² Aerosolized vaccinia virus survives 24 hours if not exposed to UV light, and the smallpox virus is predicted to behave similarly.² Because there would be a 2-week interval between release of the virus and definitive diagnosis of smallpox—the smallpox rash develops only after approximately 2 weeks of incubation—evidence of smallpox is unlikely to be found before exposed people become ill.²

Transmission of smallpox occurs through inhalation of aerosolized droplets (usually through face-to-face contact).^{2,3} Scabs, which also contain the live virus, are less infectious.² The same is true of contaminated bedding and clothing.⁵ Again, the incubation period is approximately 12 to 14 days (range, 7–17 days) after exposure,^{4,5,7} during which time there is no viral shedding and the person feels healthy and is not contagious.⁵ Initial sudden-onset symptoms include fever, headache, fatigue, backache, and, occasionally, delirium and abdominal pain.^{2,4,5,7,8} Within 2 to 3 days, the fever drops, and a characteristic rash develops on the head and extremities.^{3,5,7} This rash consists of small erythematous macules that grow to 2- to 3-mm papules, then to 2- to 5-mm vesicles, and last to 4- to 6-mm pustules.³ Vesicles developing in the oral mucosa ulcerate quickly and release large amounts of infectious virus into the saliva.^{2,3}

Persons with smallpox are infectious to face-to-face contacts after fever begins and during the first week of the rash, when the virus is released into the respiratory tract.^{2,5} The period of highest contagiousness usually coincides with the person's being bedridden with rash, high fever, and malaise.² As a result, relatives of the infected person are usually the next people to contract the disease.² A person remains infectious until the last of the scabs fall off; fortunately, though, someone exposed to the person at this time is less likely to become infected.⁵

Smallpox Rash

Erythematous macules develop first in the mouth. Within 1 to 2 days, these lesions vesiculate, rupture, and release large amounts of virus.² An erythematous maculopapular rash then spreads to the face, forearms, trunk, and legs.^{2,3,7} The monomorphic lesions of this rash progress from macules to papules.^{3,5} After 1 to 2 days, the rash vesiculates, and pustules form. These firm-looking pustules become deeply embedded in the dermis.² On day 8 or 9, crusts form; after 3 to 4 weeks, the crusts separate,^{4,7} and pitted scars develop.^{2,3} Scarring, which can be severe, affects 65% to 80% of

infected individuals.^{3,7} Ninety percent of smallpox cases have this characteristic presentation.

There are other less common presentations of smallpox. Variola minor is a less severe form of smallpox and is possibly a subspecies of variola.⁷ With variola minor, the rash is less severe, and there are fewer systemic symptoms. Milder symptoms occur in people with residual immunity from prior smallpox vaccination. Malignant and hemorrhagic forms of smallpox can be more difficult to diagnose because the clinical appearance is not classic for smallpox. The malignant form of smallpox can appear as red confluent lesions that are velvety, crepelike and rubbery in appearance. The lesions develop slowly and do not form pustules.^{2,5} The lesions of hemorrhagic smallpox appear first as dusky erythema, followed by petechiae and hemorrhage.^{2,5} Pregnant women may be more susceptible to smallpox in its uniformly fatal hemorrhagic form.² Some reported cases of malignant or hemorrhagic smallpox are thought to have been the result of defective immunity,² and it is not known how present-day immunocompromised individuals (those infected with the human immunodeficiency virus and those receiving chemotherapy) would respond to smallpox infection. Secondary bacterial infection is possible, and encephalitis occurs occasionally.² Death results from overwhelming release of soluble variola antigens and immune complexes,^{2,3} pulmonary edema secondary to heart failure,⁷ or hypotension.³ On day 6 of the rash, neutralizing antibodies appear and remain in high titers for many years.^{2,3}

Clinically, distinguishing smallpox from chickenpox^{3,7} (varicella zoster virus) can be difficult because both cause widespread erythematous vesicles and pustules that crust. However, there are differences between the 2 diseases that can help in the diagnosis. Smallpox lesions tend to be acral and are all in the same stage at the same time, whereas chickenpox lesions tend to be truncal and appear as crops of vesicles that are in different stages (papule, vesicle, crust) at the same time. In addition, smallpox lesions (deep-seated pustules) appear on the palms and soles, whereas chickenpox lesions almost never appear there.²

Laboratory Diagnosis

For laboratory confirmation of smallpox, a pustule is opened with a scalpel, and material is collected with a cotton swab.² Scabs can be removed with forceps.² The infected material should be transported in a vacutainer sealed with tape and enclosed in a waterproof container.² Local health officials should be contacted regarding transport of the specimens;

high-level (BL-4) containment is required.² The specimen should be collected by someone who has been vaccinated (even vaccinated that day).² Infection can be confirmed by electron microscopic examination of pustular fluid.^{3,7} Results of silver impregnation or fluorescent antibody staining of smears also can confirm the diagnosis.⁷ A 4-fold rise in smallpox antibody titer and examination of cultured tissue also confirm smallpox infection.⁷ Enzyme-linked immunosorbent assay and polymerase chain reaction diagnostic techniques for confirming the diagnosis have been under development since January 2000.³ Last, smallpox isolated on live cell culture also confirms the diagnosis.³

Various agencies are validating tests for smallpox virus in the environment.⁹ Environmental disinfection involves use of hospital-grade disinfectants (quaternary ammonias), which are effective in killing the virus on surfaces. Bleach is also an effective disinfectant.

Treatment

During an outbreak of smallpox, containing the spread of the disease⁵ and providing supportive care^{3,7} are essential. People with smallpox are not infectious in the incubation phase and become contagious only when fever and rash develop.⁵ Those diagnosed with smallpox should be isolated, and all their close contacts should be vaccinated within 4 days of exposure.^{1-3,5,9} Immunity develops rapidly after vaccination, and vaccine administered within 4 days after exposure provides protective immunity, which can prevent infection or lessen the severity of the disease.⁵

Patients should be isolated at home, as smallpox can spread rapidly through a hospital ventilation system.^{2,3,5,8} In addition to vaccination and isolation, the patient's close contacts (household members, face-to-face contacts) should have their temperature taken daily (they are not contagious until onset of the rash).² A person who has a temperature reading higher than 38°C (101°F) within 17 days after being exposed should undergo further testing for smallpox infection.²

Vaccine immune globulin (VIG) is indicated for severe cutaneous reactions from vaccination and for protecting people who need to be vaccinated but who are at risk for complications from vaccine. Approximately 250 of 1 million people vaccinated would experience an adverse reaction requiring VIG.² Secondary bacterial infection of the vaccination site can be treated with antibiotics.

There is no known antiviral treatment for smallpox, but cidofovir might prevent smallpox infection if administered within 1 to 2 days after

exposure.^{2,3} Cidofovir is under investigation for use in treating smallpox^{5,10} because it is highly active against 3 isolates of variola.¹¹ In a medication prophylaxis study using a murine model, mice were protected by a single high dose of cidofovir (100 mg/kg) given within 16 days before viral challenge.¹¹ There was no evidence of renal or hepatic toxicity with this single dose.¹¹ Cidofovir must be administered intravenously.¹¹ Corneal lesions may be treated with topical idoxuridine.³ Supportive care and adequate nutrition and hydration are required; secondary infections should be treated with antibiotics.³

Vaccine

Smallpox vaccine contains live vaccinia virus, an *Orthopoxvirus* closely related to variola virus. Immunity to vaccinia protects against smallpox.⁵ Approximately half the US population has never been vaccinated for smallpox.⁹ Duration of immunity and immune status of persons vaccinated 30 years ago are not known for certain, and individuals who had a single-dose vaccination when they were children are not likely to have lifelong immunity.² Estimates of duration of immunity vary from 10 years⁵ to only 3 to 5 years.⁹ Even when immunity has waned, however, previously vaccinated persons who develop smallpox shed less virus and are less infectious.⁵ For people exposed to smallpox, vaccine given within 4 days after exposure can lessen the severity of or even prevent smallpox.^{3,9}

Vaccine Complications—Vaccine complications include encephalitis, progressive vaccinia, eczema vaccinatum, generalized vaccinia, inadvertent inoculation, and other nonspecific eruptions.^{2,5,12} Certain groups are considered to be at high risk for vaccination complication—pregnant women and patients with eczema or exfoliative skin conditions; hereditary immune disorders; leukemia, lymphoma, or generalized malignancy treated with alkylating agents, antimetabolites, high-dose steroids, or radiation; and HIV infection.^{2,5} If a person with one of these contraindications is a close contact of a smallpox patient, vaccine and VIG should be coadministered. If VIG is not available, vaccination should be performed anyway because an adverse outcome is more likely with smallpox than with vaccination.²

Conclusion

The release of smallpox virus would be a worldwide catastrophe. Although many people think that the threat is not likely to become a reality, preparations have been started so that we will be able to respond

to any use of biological weapons in any form, including smallpox. Dermatologists should continue their vigilance and remain current on possible manifestations of all chemical and biological weapons, as, sadly, these weapons have become part of our reality.

Editor's Note—Photographs of smallpox are viewable on the web at <http://www.bt.cdc.gov/agent/smallpox/index.asp>.

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